REMARKS

Claim 9 is pending in the instant application.

Claim 9 has been rejected under 35 U.S.C. § 103 as being unpatentable over Bowes et al. (Neurology 1995) in view of Mulligan et al. (Amer. Pathol. 1993) or Panes (Amer. Physiol. 1995), and Muzykantov et al. (BBA 1986), Runge et al. or Torchilin.

Claim 9 has been amended. Support for amendment to claim 9 can be found in the specification, for example at page 4, line 30 through page 5, line 19, and page 7, line 11 through page 9, line 8. No new matter is added by this amendment.

Reconsideration and withdrawal of this rejection is respectfully requested in light of these amendments and the following remarks.

Applicants respectfully disagree with the Examiner's characterization of the prior art teachings as solving a "similar problem" to the instant invention.

In an earnest effort to clarify distinctions of the present invention over the cited combination of prior art, Applicants have amended claims 9 to state that the method is for dissolution of fibrin clots in the pulmonary vasculature of an animal and that the non-internalizable antibody to ICAM-1 conjugated to an anti-thrombotic agent is systemically administering to an animal so that the non-

internalizable antibody to ICAM-1 conjugated to an anti-thrombotic agent binds to the luminal surface of the pulmonary endothelium of the animal and therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature. Support for this amendment can be found throughout the specification and in particular at page 4, line 30 through page 5, line 19, and page 7, line 11 through page 9, line 8.

In contrast, teachings of Bowes et al. relate to methods for preventing neurologic damage occurring in the reperfusion phase of ischemic-reperfusion injury. As taught at page 816, col. 1, of Bowes et al. substantial evidence indicates the prevention of leukocyte adhesion improves neurologic outcome in animal models of stroke. Bowes et al. examined the ability of monoclonal antibodies against ICAM-1 to prevent leukocyte adhesion to the vascular endothelium thereby reducing neurologic injury at brief postischemic delays and increase the postembolization interval at which thrombolysis was effective. Increased efficacy for tPA reported by Bowes is thus suggested to relate to the prevention of leukocytes adhesion by separate administration of anti-ICAM-1 antibody increasing the postischemic duration at which thrombolytic therapy remains effective. There is nothing in this reference suggesting conjugation of the anti-ICAM-1 antibody to tPA. In fact, in the experiments of

Bowes et al. tPA was administered 2 hours after administration of the anti-ICAM-1 antibody. Further, timing of administration of the subsequently administered tPA appears to be crucial to the observed efficacy as an earlier publication by Bowes et al. reported a combined therapy of an anti-ICAM-1 antibody administered 5 minutes following ischemia and tPA administered either 30 minutes or 90 minutes following ischemia to be no more effective than either substance alone at reducing neurologic damage and a combined therapy of anti-ICAM-1 antibody administered 5 minutes following ischemia and tPA administered 3 hours following ischemia to be ineffective at reducing neurological damage (Bowes et al. Exp. Neurology 1993 119:215-219).

The Bowes references and its lack of relevance to the instant claimed invention is also discussed in paragraph 5 of a Declaration by inventor Muzykantov. As made clear in this paragraph, those of skill in this art field view the subject matter of Bowes involving administration of two separate proteins (anti-ICAM and tPA), which act independently as totally different from the instant invention wherein an anti-thrombotic agent is conjugated with anti-ICAM in a way that these two entities now became a new, single entity with features different from those of both individual components.

Thus, contrary to the Examiner's suggestion there are multiple differences between the instant claimed invention and the teachings of Bowes et al. including, but not limited to, the fact that Bowes et al. is related to prevention of neurologic damage caused by post-ischemic reperfusion as opposed to fibrin clot dissolution, is unrelated to targeting a drug to the pulmonary vasculature, and actually teaches away from any expectation of successful simultaneous administration of an anti-thrombotic agent and anti-ICAM, such as the tPA/anti-ICAM-1 antibody conjugate described in this invention.

The secondary references cited by the Examiner in this rejection fail to remedy the deficiencies in this primary reference as none teach a method for dissolution of fibrin clots in the pulmonary vasculature wherein the antibody-anti-thrombotic agent conjugate binds to the luminal surface of the pulmonary endothelium of the animal and the therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature.

Instead, as acknowledged by the Examiner at page 3 of the Office Action, Runge et al. directed a thrombolytic agent tPA to the site of a thrombus by conjugation of the tPA to an anti-fibrin monoclonal antibody and Torchilin teach targeted accumulation of thrombolytic enzymes in the regions of thrombus location.

Further, contrary to the Examiner's suggestion, Muzykantov et al (1986) does not generally teach targeting of fibrinolytic agents to any regions of the vascular bed having increased probability of clot formation. Instead, Muzykantov et al. (1986) disclosed an anti-collagen antibody-erythrocyte-streptokinase complex designed to deliver fibrinolytics to the extravascular sub-endothelial interstitium, which is inaccessible for blood under normal and most pathological conditions (except rare conditions associated with overt disruption of the integrity of a blood vessel causing internal bleeding).

Thus, neither Runge et al. Torchilin or Muzykantov teach a method for fibrin clot dissolution in the pulmonary vasculature wherein the antibody-anti-thrombotic agent conjugate is targeted not at the thrombus, but rather at the pulmonary vasculature.

Finally, the Examiner has acknowledged that references cited by the Examiner relating to ICAM and anti-ICAM antibodies, namely, Panes et al. and Mulligan et al. are silent with respect to internalization of these antibodies. The Examiner suggests that nevertheless "it would be immediately apparent to one skilled in the art that the accumulation of the antibody in the pulmonary vasculature is due to non-internalization of said antibody". Applicants

respectfully submit herewith a Declaration by inventor Muzykantov, one highly skilled in the field of immunotargeting to the pulmonary endothelium, providing a summary of evidence to the contrary. As discussed in paragraph 3 of Dr. Muzykantov's Declaration, it is well known for most studied targets (including tumors, tumor vasculature, brain and peripheral vascular targets), that internalizable antibodies show markedly higher accumulation as compared to non-internalizable one. More importantly, as also discussed in paragraph 3 of Dr. Muzykantov's Declaration, accumulation in pulmonary vasculature, among all antibodies with characterized internalizability, only internalizable antibodies such as anti-ACE, anti-selectin and anti-caveoli accumulated in the pulmonary vasculature after intravascular injection. This is supported by references discussed in paragraph 4 of Dr. Muzykantov's Declaration and attached thereto as Exhibit A through . Further, as discussed in paragraph 4 of Dr. Muzykantov's Declaration, the non-internalizable anti-PECAM antibody does not accumulate in the pulmonary vasculature in animals unless it converted into an internalizable antibody. This is supported by referenced discussed in paragraph 4 of Dr. Muzykantov's Declaration and attached thereto as Exhibits of and G. Thus, contrary to the Examiner's suggestion, the fact that anti-ICAM accumulates in the pulmonary vasculature

would actually lead those skilled in the art to expect that the antibody was internalized. Further, contrary to the Examiner's suggestion, the teachings of Mulligan et al. regarding accumulation of anti-ICAM antibody in the pulmonary vasculature would actually lead those skilled in the art away from use of anti-ICAM antibody in the present invention wherein internalization is expressly taught to be undesirable.

In addition, references of Panes and Mulligan are silent with respect to any teaching whatsoever of a method for fibrin clot dissolution, conjugation of a therapeutic agent to an anti-ICAM antibody or binding of an anti-thrombotic agent to the luminal surface of the pulmonary endothelium of the animal via conjugation to an anti-ICAM antibody so that therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature.

Thus, the cited combination of references (the primary reference of which is related to use of two non-conjugated individual agents, anti-ICAM and tPA administered separately at different times, for preventing neurologic damage following post-ischemic reperfusion, not fibrin clot dissolution, and teaches away from simultaneous administration of an anti-ICAM-1 antibody and an anti-thrombotic agent and the secondary references of which

provide no teaching whatsoever of targeting a therapeutic agent to the luminal surface of the pulmonary endothelium of the animal via conjugation to an anti-ICAM antibody so that therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature and actually teach way from the expectation of anti-ICAM antibody being non-internalized) clearly provides no suggestion or motivation, either in the combination of references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings to arrive at the instantly claimed method for fibrin clot dissolution. Further, this combination of references (the primary reference of which is related preventing neurologic damage following post-ischemic reperfusion, not fibrin clot dissolution, and teaches away from simultaneous administration of an anti-ICAM-1 antibody and an anti-thrombotic agent and the secondary references of which provide no teaching whatsoever of targeting a therapeutic agent to the luminal surface of the pulmonary endothelium of the animal via conjugation to an anti-ICAM antibody so that therapeutic action of the anti-thrombotic agent is localized in the blood compartment of the pulmonary vasculature and actually teach way from the expectation of anti-ICAM antibody being non-internalized) provides no reasonable

expectation of success with respect to the instantly claimed method for fibrin clot dissolution. Finally, the prior art references when combined neither teach or suggest all the claim limitations, namely a method for fibrin clot dissolution in the pulmonary vasculature which involves administering non-internalizable antibody to ICAM-1 conjugated to an anti-thrombotic agent so that the non-internalizable antibody to ICAM-1 conjugated to an anti-thrombotic agent binds to the luminal surface of the pulmonary endothelium of the animal thus localizing the therapeutic action of the anti-thrombotic agent to the blood compartment of the pulmonary vasculature.

Thus, the cited combination of prior art references fails to meet the basic criteria of prima facie obviousness as set forth in MPEP § 2143.

In addition, the suggestion by the Examiner to modify the teachings of the primary reference of Bowes et al., which clearly requires separate administration of anti-ICAM-1 antibody and tPA at different times, specifically a two hour separation in administration of the antibody and the anti-thrombotic agent, would not only change the principle of operation of the primary reference but also very likely render the reference inoperable for its intended purpose, namely preventing neurologic damage occurring in the reperfusion phase of ischemic-reperfusion injury. Support

for this suggested modification of simultaneous administration of the antibody and tPA as a conjugate rendering the Bowes et al. reference inoperable for its intended purposes is set forth in Bowes et al. Exp. Neurology 1993 119:215-219. Thus, in accordance with MPEP § 2143.01, there can be no suggestion or motivation to make this proposed modification.

Applicants respectfully submit that it is only with the instant application in hand, that the Examiner can look back with hindsight at these disparate teachings relating to preventing leukocyte adhesion and neurologic damage from post-ischemic reperfusion injury with an anti-ICAM-1 antibody, targeting the thrombus itself or collagen in the extravascular interstitium, and general expression of ICAM-1 in the pulmonary vasculature, to arrive at a conclusion that the invention is obvious. Such hindsight, inclusive of knowledge gleaned only from applicant's disclosure, is impermissible. See MPEP § 2145 (X).

It is therefore respectfully requested that reconsideration of this rejection be given in light of the amendments to the claims and the above remarks and that this rejection under 35 U.S.C. 103 be withdrawn.

Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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